

Applicant : Nishino, N., et al.  
Serial No. : to be assigned  
Filed : August 31, 2001  
Title : NOVEL CYCLIC TETRAPEPTIDE DERIVATIVES AND PHARMACEUTICAL USES THEREOF

Art Unit : to be assigned  
Examiner : to be assigned

## PRELIMINARY AMENDMENT

Prior to examination of this application, Applicants respectfully request entry of the amendment and consideration of the remarks set forth herein.

- Information Disclosure Statement and Form PTO-1449
- Cited Reference WO 00/52033
- “Version with Markings to Show Changes Made”

I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner of Patents, Washington, D.C. 20231.

Michael L. Hubbard  
Typed Name of Person Signing Certificate

### AMENDMENT

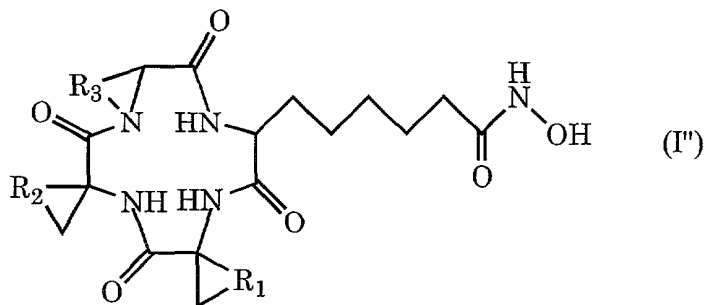
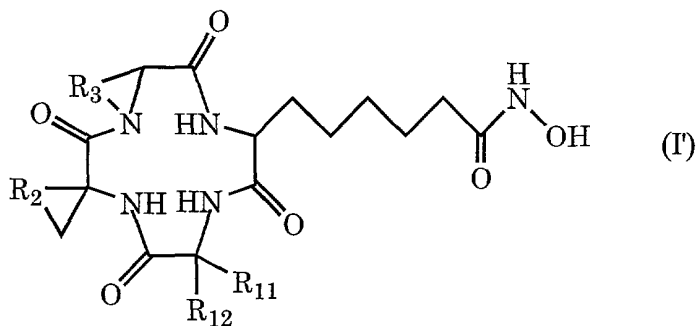
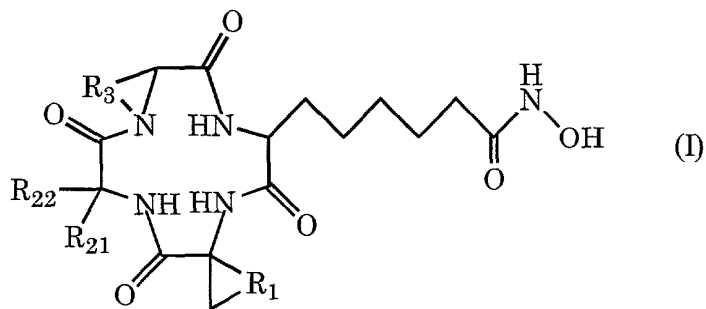
Please amend the above-captioned application as follows:

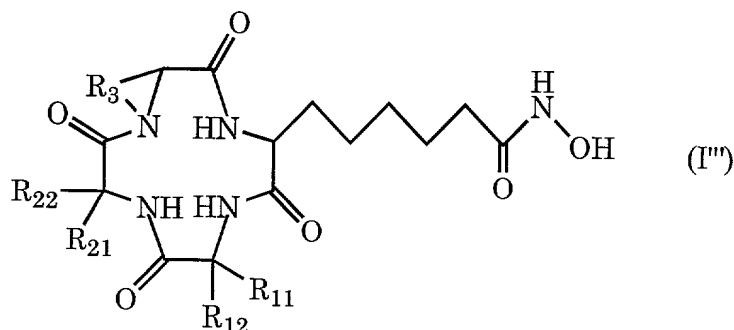
*In The Claims:*

Please cancel claims 6 and 7.

Please amend the claims as follows:

1. (Amended) A cyclic tetrapeptide derivative comprising a general formula selected from the group consisting of (I), (I'), (I''), (I''') and a pharmaceutically acceptable salt thereof:





wherein each of R<sub>11</sub>, R<sub>12</sub>, R<sub>21</sub> and R<sub>22</sub> independently denotes hydrogen, a linear C<sub>1</sub>-C<sub>6</sub>-alkyl group to which a non-aromatic cycloalkyl group or an optionally substituted aromatic ring may be attached, or a branched C<sub>3</sub>-C<sub>6</sub>-alkyl group to which a non-aromatic cycloalkyl group or an optionally substituted aromatic ring may be attached; and

each of R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> independently denotes a linear C<sub>1</sub>-C<sub>5</sub>-alkylene group which may have a C<sub>1</sub>-C<sub>6</sub> side chain, in which the side chain may form a condensed ring structure on the alkylene chain;

provided that at least one of R<sub>11</sub>, R<sub>12</sub>, R<sub>21</sub> and R<sub>22</sub> in general formula (I''') is a cyclohexyl methyl group.

2. The cyclic tetrapeptide derivative according to claim 1, comprising said general formula (I), or a pharmaceutically acceptable salt thereof.

3. The cyclic tetrapeptide derivative according to claim 1, comprising said general formula (I'), or a pharmaceutically acceptable salt thereof.

4. The cyclic tetrapeptide derivative according to claim 1, comprising said general formula (I''), or a pharmaceutically acceptable salt thereof.

5. The cyclic tetrapeptide derivative according to claim 1, comprising said general formula (I'''), or a pharmaceutically acceptable salt thereof.

8. (Amended) A pharmaceutical composition comprising a cyclic tetrapeptide derivative or a pharmaceutically acceptable salt thereof as set forth in claim 1.

Please add the following new claims:

--10. A method of inhibiting a histone deacetylase comprising administering to a subject in need thereof a cyclic tetrapeptide derivative or a pharmaceutically acceptable salt thereof as set forth in claim 1, thereby inhibiting a histone deacetylase inhibitor.

11. A method of promoting an expression of an MHC class I molecule comprising administering to a subject in need thereof a cyclic tetrapeptide derivative or pharmaceutically acceptable salt thereof as set forth in claim 1, thereby promoting an expression of an MHC class I molecule.--

0945302630

## Status of the Claims

Claims 1 to 9 are pending in the specification as filed.

In the instant preliminary amendment, Applicants canceled claims 6 and 7, amended claims 1 to 5 and 8, and added new claims 10 and 11. Thus, after entry of the instant amendment, claims 1 to 5 and 8 to 11 will be pending.

The specification sets forth an extensive description of the invention in the new and amended claims.

In view of the foregoing remarks and the instant amendment, it is believed that the all claims pending in this application (after entry of the instant amendment) are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If any additional necessary fee is required, the Commissioner is authorized to deduct such a fee from the undersigned's Deposit Account No. 06-1050. Please credit any overpayments to the above-noted Deposit Account.

Table 1. Demographic characteristics of the study population	
Age (years)	65.2 ± 1.2
Gender (male/female)	102/108
Education (years)	12.5 ± 0.5
Marital status (married/divorced/widowed)	150/30/20
Occupation (retired/working)	150/30
Income (USD/month)	1,200 ± 200
Comorbidities (hypertension/diabetes/cholesterol)	120/40/60
Medication (antidepressants/antipsychotics)	80/20
Alcohol consumption (yes/no)	30/170
Smoking status (current/former/never)	20/80/160
Family history (depression/schizophrenia)	40/20
Duration of illness (years)	10.5 ± 2.0
Previous hospitalizations (yes/no)	100/80
Current symptoms (depression/schizophrenia)	150/30
Functional status (independent/dependent)	120/80
Social support (strong/weak)	100/100
Quality of life (high/low)	120/80
Healthcare utilization (frequent/infrequent)	80/120
Adherence to treatment (yes/no)	100/80
Stress levels (high/low)	120/80
Life satisfaction (high/low)	100/100
Overall health (good/poor)	120/80
Physical activity (regular/irregular)	80/120
Dietary habits (healthy/unhealthy)	100/100
Sleep patterns (regular/irregular)	120/80
Mood stability (stable/unstable)	100/100
Thought clarity (clear/confused)	120/80
Emotional control (good/poor)	100/100
Interpersonal relationships (good/poor)	120/80
Work performance (good/poor)	100/100
Financial stability (stable/unstable)	120/80
Legal issues (yes/no)	20/180
Criminal record (yes/no)	10/190
Substance use (drugs/alcohol)	20/180
Self-harm history (yes/no)	10/190
Suicidal thoughts (yes/no)	20/180
Paranoia (yes/no)	30/170
Hallucinations (yes/no)	40/160
Delusions (yes/no)	50/150
Disorganized behavior (yes/no)	60/140
Aggression (yes/no)	70/130
Catatonia (yes/no)	80/120
Depression (yes/no)	90/110
Anxiety (yes/no)	100/100
Obsessive-compulsive (yes/no)	110/90
Tic disorder (yes/no)	120/80
Personality disorder (yes/no)	130/70
Borderline personality (yes/no)	140/60
Narcissistic personality (yes/no)	150/50
Antisocial personality (yes/no)	160/40
Psychotic personality (yes/no)	170/30
Paranoid personality (yes/no)	180/20
Schizoid personality (yes/no)	190/10
Schizotypal personality (yes/no)	200/0
Overall personality (stable/unstable)	120/80
Resilience (high/low)	100/100
Coping mechanisms (effective/ineffective)	120/80
Problem-solving skills (good/poor)	100/100
Decision-making ability (good/poor)	120/80
Communication skills (good/poor)	100/100
Interpersonal skills (good/poor)	120/80
Work skills (good/poor)	100/100
Financial skills (good/poor)	120/80
Legal skills (good/poor)	100/100
Substance skills (good/poor)	120/80
Self-harm skills (good/poor)	100/100
Suicidal skills (good/poor)	120/80
Paranoia skills (good/poor)	100/100
Hallucinations skills (good/poor)	120/80
Delusions skills (good/poor)	100/100
Disorganized skills (good/poor)	120/80
Aggression skills (good/poor)	100/100
Catatonia skills (good/poor)	120/80
Depression skills (good/poor)	100/100
Anxiety skills (good/poor)	120/80
Obsessive-compulsive skills (good/poor)	100/100
Tic disorder skills (good/poor)	120/80
Personality disorder skills (good/poor)	100/100
Borderline personality skills (good/poor)	120/80
Narcissistic personality skills (good/poor)	100/100
Antisocial personality skills (good/poor)	120/80
Psychotic personality skills (good/poor)	100/100
Paranoid personality skills (good/poor)	120/80
Schizoid personality skills (good/poor)	100/100
Schizotypal personality skills (good/poor)	120/80
Overall personality skills (good/poor)	100/100
Resilience skills (good/poor)	120/80
Coping mechanisms skills (good/poor)	100/100
Problem-solving skills skills (good/poor)	120/80
Decision-making ability skills (good/poor)	100/100
Communication skills skills (good/poor)	120/80
Interpersonal skills skills (good/poor)	100/100
Work skills skills (good/poor)	120/80
Financial skills skills (good/poor)	100/100
Legal skills skills (good/poor)	120/80
Substance skills skills (good/poor)	100/100
Self-harm skills skills (good/poor)	120/80
Suicidal skills skills (good/poor)	100/100
Paranoia skills skills (good/poor)	120/80
Hallucinations skills skills (good/poor)	100/100
Delusions skills skills (good/poor)	120/80
Disorganized skills skills (good/poor)	100/100
Aggression skills skills (good/poor)	120/80
Catatonia skills skills (good/poor)	100/100
Depression skills skills (good/poor)	120/80
Anxiety skills skills (good/poor)	100/100
Obsessive-compulsive skills skills (good/poor)	120/80
Tic disorder skills skills (good/poor)	100/100
Personality disorder skills skills (good/poor)	120/80
Borderline personality skills skills (good/poor)	100/100
Narcissistic personality skills skills (good/poor)	120/80
Antisocial personality skills skills (good/poor)	100/100
Psychotic personality skills skills (good/poor)	120/80
Paranoid personality skills skills (good/poor)	100/100
Schizoid personality skills skills (good/poor)	120/80
Schizotypal personality skills skills (good/poor)	100/100
Overall personality skills skills (good/poor)	120/80
Resilience skills skills (good/poor)	100/100
Coping mechanisms skills skills (good/poor)	120/80
Problem-solving skills skills (good/poor)	100/100
Decision-making ability skills skills (good/poor)	120/80
Communication skills skills skills (good/poor)	100/100
Interpersonal skills skills skills (good/poor)	120/80
Work skills skills	

Applicant : Nishino, N., et al.  
Serial No. : to be assigned  
Filed : August 31, 2001  
Page : 6

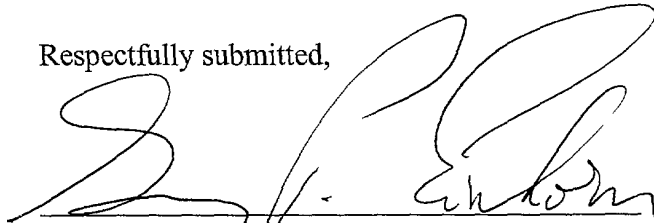
Atty's Docket No.: 08206-013001 / PH-749PCT-US

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

Date:

*Aug 31, 2001*

Respectfully submitted,



Gregory P. Einhorn  
Reg. No. 38,440

Fish & Richardson P.C.  
4350 La Jolla Village Drive, Suite 500  
San Diego, California 92122  
Telephone: (858) 678-5070  
Facsimile: (858) 678-5099

10131279.doc

PH-749PCT-US

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

Applicant : Nishino, N., et al.

Art Unit : to be assigned

Serial No. : to be assigned

Examiner : to be assigned

Filed : August 31, 2001

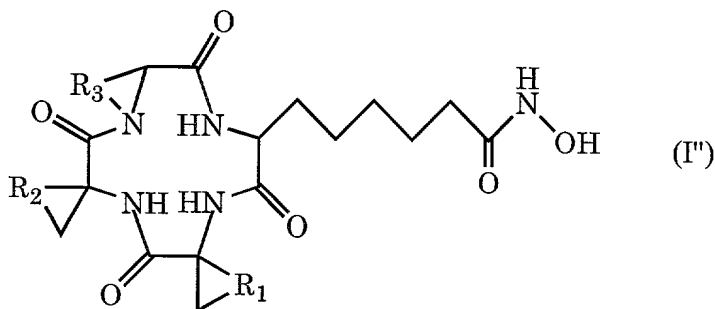
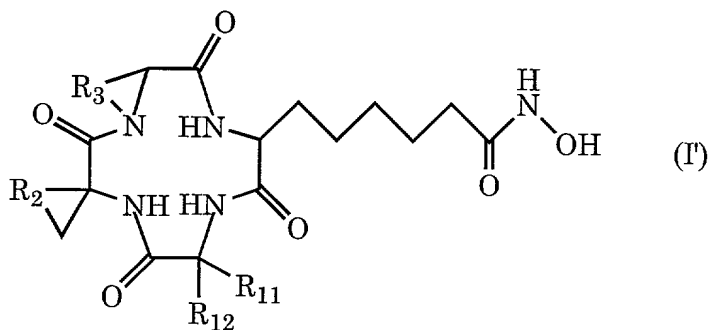
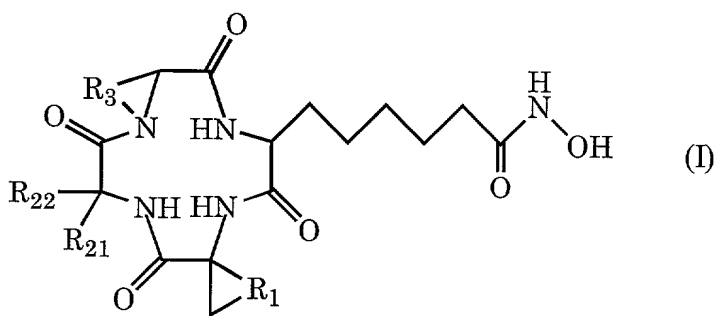
Title : NOVEL CYCLIC TETRAPEPTIDE DERIVATIVES AND  
PHARMACEUTICAL USES THEREOF

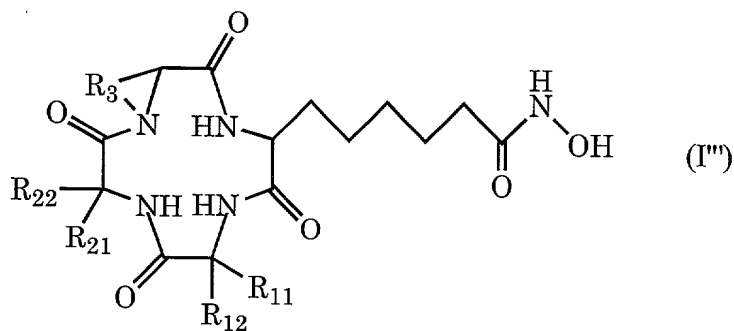
*In The Claims:*

Claims 6 and 7 have been canceled.

Claim 1 has been amended as follows:

1. (Amended) A cyclic tetrapeptide derivative comprising a [represented by the following] general formula selected from the group consisting of (I), (I'), (I''), (I''') [or] and a pharmaceutically acceptable salt thereof:





wherein each of R<sub>11</sub>, R<sub>12</sub>, R<sub>21</sub> and R<sub>22</sub> independently denotes hydrogen, a linear C<sub>1</sub>-C<sub>6</sub>-alkyl group to which a non-aromatic cycloalkyl group or an optionally substituted aromatic ring may be attached, or a branched C<sub>3</sub>-C<sub>6</sub>-alkyl group to which a non-aromatic cycloalkyl group or an optionally substituted aromatic ring may be attached; and

each of R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> independently denotes a linear C<sub>1</sub>-C<sub>5</sub>-alkylene group which may have a C<sub>1</sub>-C<sub>6</sub> side chain, in which the side chain may form a condensed ring structure on the alkylene chain;

provided that at least one of R<sub>11</sub>, R<sub>12</sub>, R<sub>21</sub> and R<sub>22</sub> in general formula (I''') is a cyclohexyl methyl group.

2. (Amended) The cyclic tetrapeptide derivative according to claim 1, comprising [which is represented by] said general formula (I), or a pharmaceutically acceptable salt thereof.

3. (Amended) The cyclic tetrapeptide derivative according to claim 1, comprising [which is represented by] said general formula (I'), or a pharmaceutically acceptable salt thereof.



4. (Amended) The cyclic tetrapeptide derivative according to claim 1, comprising [which is represented by] said general formula (I''), or a pharmaceutically acceptable salt thereof.

5. (Amended) The cyclic tetrapeptide derivative according to claim 1, comprising [which is represented by] said general formula (I'''), or a pharmaceutically acceptable salt thereof.

8. (Amended) A pharmaceutical composition comprising a [the] cyclic tetrapeptide derivative or a pharmaceutically acceptable salt thereof [according to any one of claims] as set forth in claim 1 [to 5 as an active ingredient].

The following new claims have been added:

10. A method of inhibiting a histone deacetylase comprising administering to a subject in need thereof a cyclic tetrapeptide derivative or a pharmaceutically acceptable salt thereof as set forth in claim 1, thereby inhibiting a histone deacetylase inhibitor.

11. A method of promoting an expression of an MHC class I molecule comprising administering to a subject in need thereof a cyclic tetrapeptide derivative or pharmaceutically acceptable salt thereof as set forth in claim 1, thereby promoting an expression of an MHC class I molecule.